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REVIEW

History and future perspectives of treating asthma as a systemic and small airways disease

L. BJERMER

Department of Lung Medicine, University Hospital, Trondheim, Norway

Abstract Asthma is an inflammatory disorder in which the small airways of the lung play an important role. There is also evidence for the systemic nature of asthma. No current method adequately measures small airways function alone. Therefore, a combination of functional and clinical parameters should be used to ensure that patients with asthma are adequately treated with due consideration of the small airways. Previously, therapeutic strategies have focused on bronchodilation and attenuation of airway inflammation. While early oral therapies had the advantage of reaching the small airways and treating the systemic aspect of asthma, they were associated with serious side-effects. Inhaled therapies were therefore developed to limit these effects. However, inhaled therapies have the disadvantage of limited penetration into the peripheral airways and an inability to treat the systemic component of asthma. They are also associated with local and systemic side-effects. The future for asthma treatment is likely to be a systemically administered medication with few side-effects targeting disease-specific mediators. The leukotriene receptor antagonists and anti-IgE monoclonal antibodies are examples of such therapies and the emergence of other new strategies is awaited.

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Keywords asthma; inflammation; small airways; systemic; leukotriene receptor antagonists.

INTRODUCTION

Asthma is one of the most common respiratory diseases and its prevalence is increasing in developed countries. Treatment for asthma has been available for centuries, with ancient Egyptian, Hebrew and Greek writings all referring to the condition. The Ebers Papyrus (1550 BC) refers to the treatment of a respiratory condition, which was probably asthma, with herbs, enemas and the administration of animal excrement (1). The Chinese were also familiar with asthma and early writings (1000 BC) mention inhalations using plants that have in modern times been found to contain the adrenergic agent ephedrine (2). Homer used the term 'asthma' in the *Iliad* to denote panting or distressed breathing. Hippocrates also viewed asthma as a similar syndrome (3).

Aretaeus (2nd century AD) of Cappadocia provided the first recognizable clinical descriptions of asthma as a disease and not merely a symptom. He described the symptoms of asthma as '. . . a heaviness of the chest, sluggishness to one's accustomed work and to every other exertion, difficulty in breathing on a steep road . . .' and '. . .during the remissions, though they may walk erect, they hear the traces of the affection' (4). However, despite this recognition of asthma as a distinct condition, for many years it was still treated as a symptom rather than a disease.

Records from the 16th century document the treatment of John Hamilton, Archbishop of St Andrews, Scotland who had severe asthma. His physician recommended, among other things, avoiding the use of feathers in his bed (5). In the 17th century, Jean van Helmont, who suffered from asthma himself, described asthma as a 'drawing together of the bronchi.' He also provided the earliest reference to the aetiology of an attack in his description of a monk who 'as oft as any place is swept or the wind doth otherwise stir up the dust, he presently falls down almost choked' (6).

William Osler (1849–1919) made the first reference to inflammation in the pathogenesis of asthma when he in-

Correspondence should be addressed to: Prof. Leif Bjermer M.D., Department of Lung Medicine, University Hospital, 7006 Trondheim, Norway. Fax: +47 73 867 424; E-mail: leif.bjermer@medisin.ntnu.no

cluded the elements of mucosal oedema and obstructing mucus into his model of the asthmatic process (7). In 1879, Ehrlich observed eosinophils in the sputum of patients with asthma, although from his book it would appear that Henry Hyde Salter (1823–1871) might have noted the presence of eosinophils sometime before this (7).

In the early 1800s, asthma relief was reportedly achieved through the smoking of leaves from *Datura* plants (8), which are now known to contain anti-cholinergic alkaloids. However, despite the wealth of historical knowledge about asthma and its treatment, and the gradual realisation that it is a distinct disease with a specific set of causes and clinical consequences, there was very little understanding of the pathogenesis of asthma or its treatment until the early 1900s.

DEVELOPMENT OF THE UNDERSTANDING OF ASTHMA PATHOGENESIS

Asthma as an inflammatory lung disorder

Asthma was initially regarded as an abnormal contractility of the smooth muscles in the airways, as illustrated by the 1962 American Thoracic Society definition (9). Bronchial asthma was recognized by

> 'recurrent episodes of airflow limitation that are usually reversible either spontaneously or with appropriate treatment' (9).

However, improved understanding of the disease process has altered our view of asthma and it is now considered mainly as an inflammatory airway disorder, associated with heightened airway responsiveness to a variety of bronchial stimuli (10). Post-mortem studies have subsequently provided supporting evidence for the concept that airway inflammation is the key process in asthma (11–16).

The latest Global Initiative for Asthma (GINA) guidelines define asthma as

> 'a chronic inflammatory disorder of the airways in which many cells play a role, in particular mast cells, eosinophils, and T-lymphocytes' (17).

This inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough particularly at night and/or in the early morning. These symptoms are usually associated with widespread but variable airflow limitation that is at least partly reversible either spontaneously or with treatment. The inflammation also causes airway hyper-responsiveness to a variety of stimuli (17).

An active inflammatory process is present, even in the asymptomatic patient. Chronic inflammatory reactions are central to the disease process and underlie the functional airway abnormalities and airflow limitation in asthma. Chronically inflamed airways are associated with remodelling, and airways become hyper-responsive and obstructed as airflow is limited by smooth muscle contraction, fibrosis, oedema, excess mucus production and infiltrating inflammatory cells. Thus, uncontrolled inflammation in asthma leads to bronchoconstriction and hyper-responsiveness.

The recognition of asthma as an inflammatory disorder was a major breakthrough in the history of treating this disease, shifting the focus of treatment from bronchodilating to anti-inflammatory drugs. The goal of any asthma treatment should be to suppress airway inflammation and modify progression of the disease as this strategy has potential long-term implications for improving the morbidity of asthma.

Asthma as a systemic disorder

Evidence suggests that different regions of the airways are pathophysiologically linked (18), with inflammation arising in regions from the nose to the alveoli. In addition, the presence of inflammatory mediators in the circulation provides support for the systemic nature of asthma.

Asthma and rhinitis

Asthma and allergic rhinitis often co-exist (19–21). Approximately 20% of children with allergic rhinitis later develop asthma or wheezing (22) and the converse also applies. For example, 50% of patients with asthma develop allergic rhinitis (23).

The pathophysiological link between the upper and lower airways is supported by several observations. First, the prevalence of bronchial hyper-responsiveness is higher in patients with allergic rhinitis compared with normal subjects despite a lack of clinical evidence of asthma (24–27). Second, patients with perennial rhinitis show increased levels of bronchial hyper-responsiveness compared to those with seasonal rhinitis (28,29). Finally, bronchial hyper-reactivity in patients with seasonal rhinitis increases during the allergen season and decreases during the 'off-season' (30–32).

There is also support for a link between the upper and lower airways in non-atopic asthma. Eosinophils have been identified in the nasal mucosa of asthmatic patients even in the absence of rhinitis, and these findings provide further evidence for asthma and rhinitis being clinical expressions of the same disease process (33).

These findings are substantiated by studies examining levels of exhaled nitric oxide. In patients with asthma, allergen-induced inflammation is associated with elevated exhaled nitric oxide concentrations (34). This has led to the proposal of exhaled nitric oxide as an indirect marker

of lower airway inflammation in asthma (35). The concentration of exhaled nitric oxide is increased in hyperresponsive subjects, and decreases significantly after methacholine-induced bronchoconstriction, suggesting that nitric oxide production occurs in the peripheral airways (32). Patients with allergic rhinitis also have increased levels of exhaled nitric oxide indicating an ongoing inflammatory activity in the lower airways (32,36).

The marked infiltration of eosinophils into affected tissues during allergic inflammation is a clinical feature associated with asthma, allergic rhinitis and atopic dermatitis. However, there is now also considerable evidence that the bone marrow plays an integral role in allergic inflammation (37).

Asthma and bone marrow connection

In asthma, allergen exposure in the airway activates a systemic response that provokes inflammatory cell production by the bone marrow (38). Bone marrow progenitor cells proliferate and differentiate, leading to a persistent increase in the numbers of mature basophils, eosinophils and mast cells in both the circulation and airway tissues (39–42). These observations provide further support for the proposition that asthma is a systemic disease (37). Basophils and eosinophils play a significant role in promoting allergic inflammation (43–45), and in allergic subjects these cells are increased and activated compared with non-atopic control subjects.

T-cell recruitment to the lungs is thought to play a key role in airway inflammation. Current understanding suggests that the local airway eosinophilia and IgE-dependent mast cell activation characteristic of asthmatic inflammation are regulated by cytokines derived from type 2 T-helper lymphocytes (Th_2 T cells). T_2 cells co-ordinate and amplify the effector functions of antigen-specific and non-specific proinflammatory cells such as B cells and eosinophils. The Th_2 cells in particular promote allergic inflammation though proinflammatory cytokines. The parallel changes in T-cell activation and cytokine production are detectable in peripheral blood as well as in the bronchial mucosa and reflect the systemic nature of asthma (46).

Asthma and atopic dermatitis

Like asthma and rhinitis, atopic dermatitis is also associated with elevated IgE, circulating T cell levels and eosinophilia (47). Additionally, 80% of children with atopic dermatitis will ultimately develop asthma or allergic rhinitis (48). A number of observations suggest that the course of asthma is affected by atopic dermatitis (47,49,50), further supporting the presence of a systemic response.

Thus, asthma should be regarded as a systemic disease sharing features with other compartments of the body as the nose, skin and bone marrow. It is difficult to achieve optimal asthma control in a patient with asthma and rhinitis without also treating the nose. The same probably applies for concomitant manifestations in other parts of the body. This view of asthma as a potential systemic disorder supports the use of systemic therapeutic modalities (46).

ASTHMA AS A DISEASE OF THE SMALL AIRWAYS

The small airways of the lung are those bronchial passages <2 mm in diameter located beyond the seventh or eighth generation of the bronchial tree and these airways account for approximately 80% of the lung total surface area (51). Asthmatic inflammation is now known to be present in the smaller airways in addition to the large central and intermediate-sized airways (18,52).

Evaluation of the small airways

In normal subjects, the small airways provide only 10% of the total airway resistance (53–55). This has led to the small airways being termed the 'silent zone' since airflow obstruction within them causes little change in the conventional tests of pulmonary function (10,53,56). However, the difficulties involved in performing physiological measurements specific for this site and *in vivo* sampling has led to the considerable under-evaluation of the small airways (57,58). Although an early study (59) suggested that the small airways are clinically 'silent' in asthma, later studies found that this is not the case (60). A study using specific airway conductance techniques (pressure-flow data) instead of spirometric measurements, found that even in mild asthma there was a seven-fold increase in peripheral airway resistance compared to healthy subjects despite the fact that pulmonary function did not differ between the two groups (60).

Functional measurements

Although small airway disease is a key feature of asthma, studies comparing central and peripheral airways suggest that the simple measurements of lung function used clinically focus more on events in the large airways. Thus, improvements in these parameters may not reflect small airway pathology (10).

Lung function

The parameters used to assess the severity of asthma include forced expiratory volume in 1 sec (FEV_1), which mainly measures large airway function (61), and peak

expiratory flow (PEF). However, clinical data suggest these measurements do not always correlate with other markers of disease activity (62). For example, while substantial improvements may occur in a number of clinically relevant non-physiological measures such as daytime symptom scores, nocturnal awakenings due to asthma, use of β_2-agonist rescue medication, quality of life and frequency of acute asthma exacerbations, only relatively modest changes in FEV_1 may be seen (Fig. 1) (63,64). This may be due to a physiological improvement in airflow obstruction in the small airways that is not reflected in the FEV_1 response (65,66). The correlation between PEF and symptoms of asthma is also poor (63).

The presence of an enhanced inflammatory process in the small airways is consistent with an increase in peripheral airway resistance (67). Direct measurement of intrabronchial pressure with a catheter-tipped micromanometer showed that while central airway resistance showed a tendency to increase in patients with bronchial asthma, only peripheral airway resistance increased significantly (67). These observations, together with the 'insensitivity' of FEV_1 in reflecting asthma outcomes, suggest the peripheral airways are an important site of airflow obstruction, irrespective of the different pathogenesis of chronic airflow obstruction.

Flow volume spirometry

In asthma patients with near normal FEV_1 and forced vital capacity (FVC) values, the change in flow rates at mid to low lung volume ($FEF_{25-75\%}$) has been shown to be significantly lower in patients with asthma (77·4% predicted) when compared with normal subjects (93·5% predicted, P=0·047) (60). This suggests that $FEF_{25-75\%}$ may be a more sensitive measure of the calibre and function of the small airways (68). Therefore, in these patients, outcomes may be better monitored using spirometric methods that pay more attention to changes in $FEF_{25-75\%}$ as an indicator of small airway function than more conventional methods (69).

In patients with more advanced disease with episodic or more persistent bronchial obstruction, $FEF_{25-75\%}$ is a less valuable measure of small airway involvement. In these patients, flow limitation in the lower airways is accompanied by areas in which complete obstruction occurs resulting in air-trapping, decreased FVC and increased residual volume (RV). Since $FEF_{25-75\%}$ is related to FVC, a substantial decrease in FVC may give a falsely high $FEF_{25-75\%}$ (Fig. 2). Thus, when flow-volume

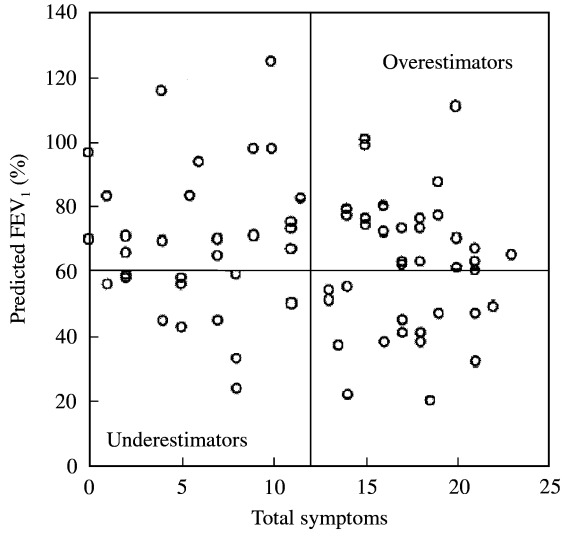

Fig. 1. Relationship between FEV_1 and symptom scores. Adapted from Teeter and Bleecker, 1998 (63).

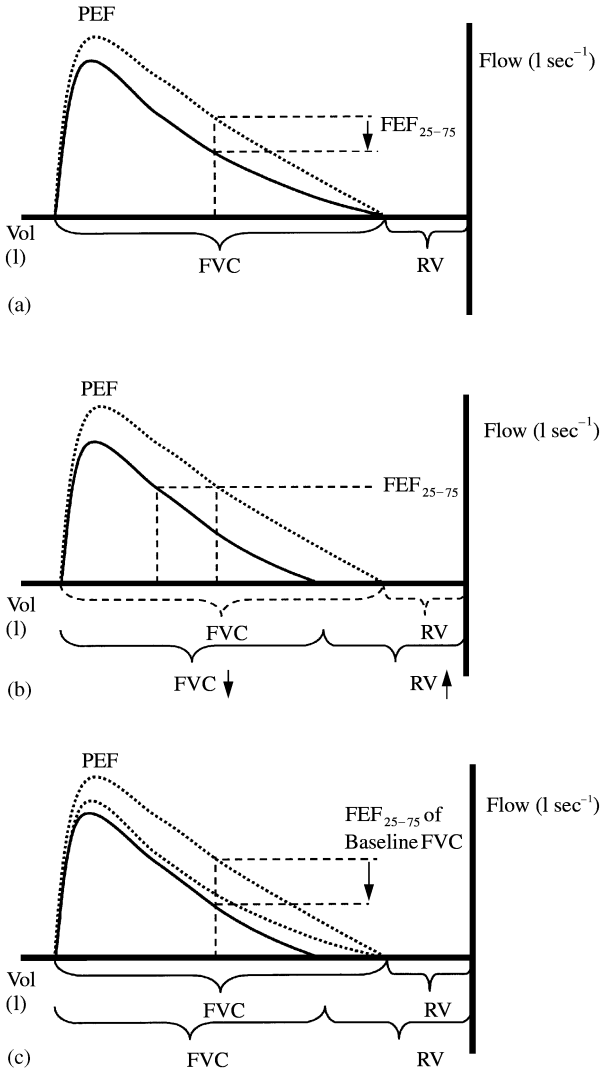

Fig. 2. Flow volume spirometery and the small airways. (a) $FEF_{25-75\%}$ represents mean flow between 25% and 75% of FVC; (b) when air trapping occurs FVC decreases (volume response), thus $FEF_{25-75\%}$ does not appropriately reflect the obstruction occurring; (c) $FEF_{25-75\%}$ is related to baseline FVC before provocation; in this situation increasing obstruction is also reflected by $FEF_{25-75\%}$ when FVC decreases after provocation.

parameters are used to evaluate small airways involvement, both FVC and $FEF_{25-75\%}$ should be considered.

In conclusion, $FEF_{25-75\%}$ may indicate small airways function in some instances, such as very mild asthma without variable FVC. However, in general, it is not a definitive measure of small airways involvement.

A number of physiological parameters that are more sensitive than FEV_1 for small airways disease have been identified (70), including measures derived from single-breath nitrogen wash-out and volume of isoflow comparing air and helium on the flow-volume curve. However, while sensitive, these are not specific for small airway disease and may also be affected by changes in large airway function. Closing volume is a more specific indicator of small airway function, but shows a high degree of inter-subject variability (71,72). Density dependence of flow measurements are sensitive indicators of peripheral airways function (73) but their utility is limited by a high degree of test–retest variability (74).

Computed tomography

High-resolution computed tomography (HRCT) scanning captures fine lung detail and can demonstrate morphological changes in the small airways associated with dysfunction that are too subtle to be identified through conventional lung function measurements alone (75–79). Advances in HRCT scanning have also made it possible to obtain non-invasive, reproducible measurements of structure–function relationships within the small airways and an *in vivo* assessment of drug deposition (76,77,80).

HRCT techniques allow measurement of the changes in regional air-trapping that accompany changes in small airways calibre (76,81). The HRCT appearance of small airways during a suspended breath-hold at residual volume (RV) comprises patchy areas of high and low attenuation of the lung parenchyma; known as 'mosaic perfusion'. This is thought to be a consequence of reflex vasoconstriction in under-ventilated areas of the lung (82). Patients suffering from moderate asthma present larger areas of air-trapping and mosaic perfusion than normal subjects, particularly in non-dependent areas of the lung (Fig. 3) (83). Air-trapping may take the form of complete obstruction (assessed using HRCT or increases in RV) or narrowing which results in reduced airflow in the peripheral airways (measured by $FEF_{25-75\%}$). A significant positive correlation exists between the amount of air-trapping and the extent of small airways alteration (83).

Air-trapping can be quantified by analysis of lung attenuation curves (LAC) at RV. A shift to the left in the LAC (i.e. to lower attenuation) represents an increase in air-trapping. Such shifts are demonstrated in patients with mild asthma after methacholine inhalation, even in the absence of any detectable change in FEV_1, indicating hyper-reactivity of the peripheral airways (76,84). A shift

Fig. 3. Example of air trapping in a patient with asthma. Adapted from Laurent *et al.*, 1998 (83).

to the right of the LAC (i.e. to higher attenuation), reflects reduced air-trapping and corresponds to an improvement in small airways calibre.

Air-trapping scores show a greater correlation with HRCT scans than with lung function tests such as FEV_1, FRC and RV (83). This suggests that HRCT scans may yield information not provided by lung function tests (83) and provides further evidence that obstruction in the small airways does not affect FEV_1.

Scintigraphy

Isotope inhalation studies provide a functional method of evaluating aerosol deposition in the lower airways. Data from such studies have shown that methacholine-induced bronchoconstriction affects drug deposition by preventing inhaled medications from reaching the lung periphery (Fig. 4) (85). Consequently, the majority of inhaled drug is deposited in the more central airways (86). This may explain why patients with asthma show less systemic availability of inhaled corticosteroids compared with normal subjects, simply because the drug does not penetrate deep enough into the lung to be systemically absorbed.

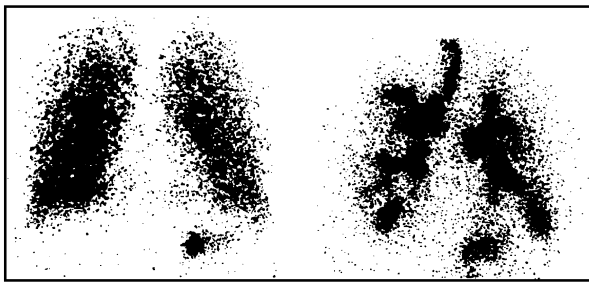

Fig. 4. Ventilation scintigraphy on a patient with baseline normal lung function, before and after metacholine provoked bronchoconstriction. Bronchoconstriction leads to an increased amount of drug being deposited in the central compared to the peripheral parts of the airways. Adapted from Laube *et al.*, 1986 (85).

Morphological measurements

Techniques such as transbronchial biopsy, bronchoalveolar lavage, post-mortem tissue analysis and levels of exhaled nitric oxide have all indicated that extensive mucosal inflammation occurs in the small airways. Recent studies confirm these morphological findings and demonstrate the presence of significant small airway inflammation in asthma (18,87,88). Asthma is associated with an increase in T cells and total and activated eosinophils in all airways, compared with patients without asthma ($P < 0{\cdot}001$) (18). However, in asthma, the number of activated eosinophils present in the small airways is significantly greater than in the large airways ($P < 0{\cdot}05$) (18). These results are indicative of the presence of a more severe inflammatory process in the peripheral airways than in the large central airways, which is consistent with the smaller airways being a major site of pathology in asthma (18,89). The presence of greater numbers of eosinophils in small airways compared with the large airways and parenchyma has also been confirmed by histochemical staining (18,90). These findings are further supported by a computational analysis based on quantitative histology, which showed that the peripheral airways account for the majority of the airway hyper-responsiveness in asthma (91,92).

There are also differences between the airways regarding the location of eosinophils within them. The small airways have a preponderance of eosinophils in their 'outer' region (between smooth muscle and alveolar attachments), while in large asthmatic airways the greatest density of eosinophils lies in the 'inner' region (between basement membrane and smooth muscle) (93). The increased T cell accumulation and eosinophil activation seen in the small airways suggest that inflammation at this site is a key feature of the pathogenesis of asthma. This difference in the location of eosinophils in the large and small airways may have implications when anti-inflammatory treatment is given via the inhaled route. Effective treatment of inflammation situated deeper in the tissue should theoretically require a higher dose of inhaled medication in order for the drug to penetrate into the tissue and penetration may not be complete. However, in reality the concentration of inhaled drugs is lower in the peripheral airways than in the central airways (94). A study of the distribution of inhaled fluticasone propionate showed that the concentration achieved in the peripheral airways was three to four times lower than that in the central airways (94).

Clinical correlates of small airway function

Exacerbations in asthma. Differences in the degree of small airway involvement reflected by differences in closing volume appear to distinguish between those patients with and without frequent acute exacerbations of asthma, despite similar FEV_1 values (95). Inflammatory obstruction in small airways may predispose patients to excessive airway closure and to frequent exacerbations.

Nocturnal asthma. Studies in nocturnal asthma have shown that the inflammatory response in the airways is considerably greater at night (88,96–98). The acute alteration in symptoms at night is associated with cellular infiltration and increased numbers of eosinophils and $CD4^+$ lymphocytes preferentially in the peripheral airways and alveoli rather than the proximal airways (Fig. 5) (98,99). This suggests inflammation in the peripheral airways and alveoli may be responsible for the acute worsening of the condition. The persistence of alveolar inflammation in patients with nocturnal asthma who are treated with inhaled steroids suggests that inhaled anti-inflammatory medications may not target this important area of involvement in asthma (97).

Exercise-induced asthma. Exercise-induced asthma (or exercise-induced bronchospasm) is a common condition, occurring in up to 90% of previously untreated patients with asthma (100). Current evidence suggests that the stimulus of airway cooling and/or drying is translated into airflow limitation as a result of the narrowing of the airways (101). For example, patients with exercise-induced asthma demonstrate an increase in peripheral resistance following challenge with cool, dry air which correlates with airway hyper-responsiveness (102). Subsequent studies have shown that the peripheral resistance in patients with mild asthma and exercise-induced asthma is greater than that of normal subjects. This further suggests that fewer peripheral airways are available for ventilation in these patients (103).

Decline in lung function. Chronic poorly controlled inflammation in the peripheral airways may contribute to

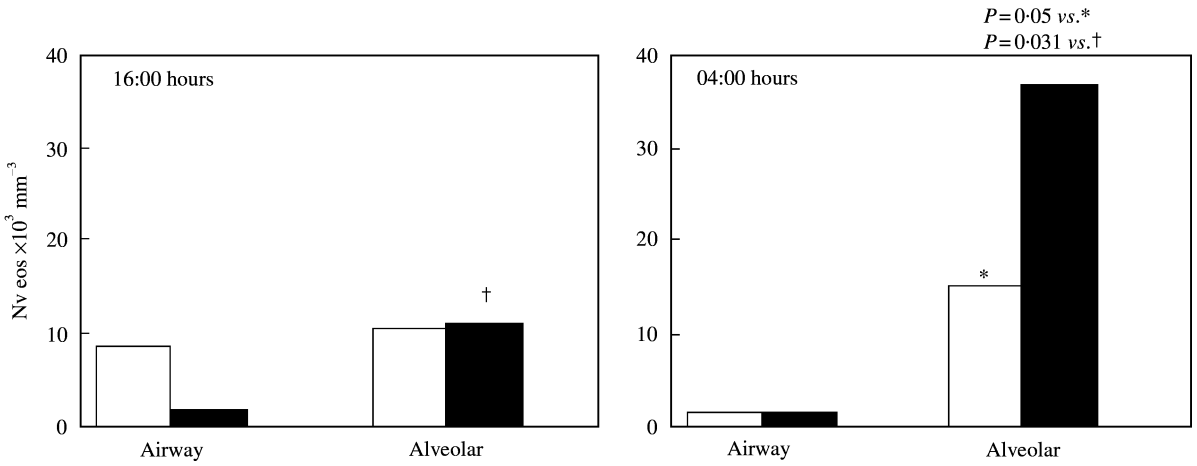

Fig. 5 The median number per volume of eosinophils in patients with nocturnal (■) and non-nocturnal asthma (□) at (a) 16.00 hours and (b) 04.00 hours. Adapted from Kraft *et al.*, 1996 (98).

the observed accelerated decline in lung function with age (104,105) and notably in patients with newly diagnosed asthma (106). A recent study has shown that neither nedocromil nor inhaled corticosteroids affect the disease progression of asthma in terms of improved lung function as measured by FEV_1 (107). Whether this is due to a lack of inflammatory control as a result of insufficient deposition in the peripheral airways or because steroids do not affect all parts of the inflammation is an open question. Similar data from long-term studies which evaluate the newer anti-inflammatory drugs, such as the leukotriene receptor antagonists, are required.

In addition to inflammation, airway remodelling (increased wall thickness, smooth muscle area and inflammatory cell inflammation) also occurs throughout the peripheral airways (16,19,88,108). A 15-year follow-up of the Copenhagen Heart Study highlighted the ongoing tissue injury and repair associated with asthma that may reduce the distensibility of the lungs (109) and adversely affect lung function as assessed by FEV_1 (104).

The structural airway changes resulting from inflammation may have more profound physiological consequences within the small distal airways than in the large proximal airways (91). Studies show evidence of increases in the thickness of the inner airway walls and inflammation of small airways in mild to moderate disease. These changes are most striking in cases that progress to chronic asthma and to fatal attacks (108). Therefore, it may be more important than previously appreciated to identify and treat inflammation at this level early in the disease process to prevent airway remodelling and progression to airway fibrosis and irreversible damage (110). Inflammation of the small airways may also cause them to act as a reservoir of inflammatory mediators, which then rise up the bronchi and provoke symptoms in the larger airways (19).

Small airways summary

Due to the challenges in evaluating the small airways, this part of the lung has not been studied to the same level of detail as the larger airways. Standard tests of lung function are probably a poor guide to small airway disease, causing the condition to be easily overlooked. Large percentage changes in peripheral resistance have a relatively small impact on airways resistance and thus, by implication on FEV_1 and PEF measurements. Both parameters are therefore unreliable reflections of events in the small airways (10).

No single method currently available is sufficiently adequate to solely measure small airways function. Therefore, an evaluation should be based on a combination of functional and clinical parameters and each patient should be treated with consideration of small airways function.

The increased T cell accumulation and eosinophil activation in the small airways show that a severe inflammatory process is present in the peripheral airways not routinely biopsied during fibreoptic bronchoscopy (18). Moreover, the low resistance of the small airways means that severe damage and obstruction can occur in these airways before symptoms occur (82). Thus, inflammation at this site is a key feature of the pathogenesis of asthma.

Because the small airways are intrinsically involved in the pathogenesis of asthma, further studies are needed to evaluate this area of the lung, particularly because of the clinical implications (111,112). Therefore, treatment in asthma needs to be directed to both the large and small airways to achieve maximal suppression of inflammation throughout the airways (88). Additionally, in the initial stages of asthma treatment should particularly target the small airways.

EVOLUTION OF MODERN PHARMACOTHERAPY FOR ASTHMA

The characterization of chronic asthma as an inflammatory condition associated with heightened airway responsiveness to a variety of bronchial stimuli, has led to the development of therapeutic strategies. These strategies have focused on bronchodilation and attenuation of airway inflammation.

Early oral therapies for asthma

The initial approach to treating asthma was via the systemic route. The advantages of this were ease of administration, reliability of drug absorption in reaching the small airways, penetration of all airways for effective asthma control and treatment of a systemic disease. The disadvantages to these early oral therapies were their serious side effect profiles and non-specific targeting of inflammatory mediators.

Oral β-agonists

Adrenal extracts were first used to treat asthma in 1900, when extracts of bovine adrenal gland were found to have benefits (113). Since then there has been an interest in the therapeutic use of the hormones produced by the adrenal gland, namely cortisol and epinephrine (114). By the 1920s, epinephrine had become the cornerstone therapy for the management of acute asthma (115). However, when β-agonists are taken orally, muscle tremor, palpitations, tachycardia and restlessness are common; and are particularly problematic in the elderly (116). These adverse effects and a slow onset of action limit their use in the treatment of asthma.

Oral corticosteroids

In 1936, Compound E was extracted from the adrenal cortex. It was renamed cortisone in 1939 and by 1950 it had been successfully used to treat asthma (117). The introduction of oral corticosteroids represented a major advance in the treatment of asthma due to their anti-inflammatory and immunosuppressive properties. However, although oral corticosteroids proved to be valuable agents for the treatment of asthma they were associated with a plethora of serious side-effects. The side-effects seen with prolonged usage include peptic ulcers, osteoporosis and associated fractures, glaucoma, hyperglycemia, skin thinning and bruising, mental disturbances (paranoia or depression with risk of suicide), muscle wasting, Cushing's syndrome, growth suppression in children, adrenal atrophy, hypertension and water retention.

Short courses of oral corticosteroids are still used to treat acute attacks of asthma since they are the most potent anti-asthmatic medications known. A high dose (e.g. prednisolone 30–40 mg day^{-1}) is administered daily for 5–7 days and then discontinued. In chronic asthma, where the patient has responded poorly to other anti-asthma agents, continued administration of oral corticosteroids may be necessary, although high doses of inhaled steroids are continued to keep the oral dose to a minimum. Thus, while oral corticosteroids have the advantage of being able to reach the small airways, chronic use may result in unacceptable side-effects (118).

Theophylline

Theophylline was originally isolated from cocoa for use in asthma therapy. Its tendency to be insoluble and emetic led to the development of a derivative aminophylline, which was more soluble. Theophylline was first used in asthma in the 1920s and aminophylline in the 1940s (2).

Theophylline is a relatively weak relaxant of airway smooth muscle. The positive effects of the drug have been attributed to a number of small beneficial effects that together may result in a favourable response. These effects are the strengthening of diaphragmatical contractility (119) increased mucociliary clearance (120) and central stimulation of the respiratory drive (121). An important advantage of theophylline is that it can be taken orally as a once- or twice-daily slow release preparation. Theophylline is particularly useful for treating patients who have more severe asthma and is also beneficial in nocturnal asthma (122–124).

The use of theophylline has become restricted in modern asthma management mainly due to the narrow therapeutic window and potential dangerous side-effects upon overdosing. Overdosing is associated with nausea, headaches and, less frequently, cardiac arrhythmia and seizures. Therefore, while theophylline is inexpensive, the need for plasma-level monitoring can be both expensive and inconvenient.

Inhaled therapies for asthma

The high incidence of severe side-effects associated with early oral therapies led to the development of inhaled therapies in an attempt to limit toxicity. However, the treatment goal was still the same: long-term suppression of airway inflammation plus relief of symptoms with quick acting bronchodilators (primarily aerosolized β_2-agonists). Current asthma therapy is predominately delivered by aerosol therapy, and inhalation devices have been improved over the years. In recent decades, attempts have been made to refine rather than change asthma therapy.

Inhaled β_2-agonists

In the early 1960s metered dose inhalers were introduced for use with adrenergic agents and isoproterenol inhalers became widely used in the management of asthma (115). However, this was followed by a rise in asthma mortality which was linked by circumstantial evidence to the use of high-dose isoproterenol inhalers (125). In 1967 β-adrenoreceptors were found to be separable into two types; β_1 (cardiac and gastrointestinal tract) and β_2 (lung and uterus). Increasingly inhaled β_2-agonists became available for the treatment of asthma.

The smooth muscle cells of the airways are presumed to be the target for β_2-agonists. These agents are by far the most useful bronchodilators used for treating acute, severe asthma and are most effective when inhaled (126). However, β_2-agonists lack an anti-inflammatory effect and so do not relieve the airway inflammation central to the pathogenesis of asthma.

Inhaled short-acting β_2-agonists such as albuterol and terbutaline provide rapid symptomatic relief. When used at the recommended dosages, these agents have few side-effects. However, concern exists about the use of excessive doses (127) since high doses are associated with an increased risk of death and morbidity from asthma (128–130). It has been subsequently recommended that inhaled β_2-agonists should only be used when needed and that the goals of treatment are to reduce the need to a minimum (131).

In addition, tolerance may develop to the anti-asthmatic effects of β_2-agonists (132,133), although there is little evidence for loss of their bronchodilator effects. With the introduction of long-acting β_2-agonists such as salmeterol and formoterol, this treatment approach is being increasingly used in the long-term management of chronic asthma. The addition of a long acting β_2-agonist to inhaled corticosteroids has proven beneficial in improving asthma control, including reducing nocturnal asthma and the frequency of exacerbations, in adults with chronic asthma (134). However, it has been difficult to document the same beneficial effect in children (135,136). As with the short-acting β_2-agonists, regular use of long-acting β_2-agonists has been associated with the development of tolerance and loss of protection after a short period of regular use. Tolerance is most commonly seen with triggers that operate via mast-cell activation, such as adenosine, allergens and exercise. However, studies have shown a reduced rather than loss of protection (137–139).

Anti-cholinergic bronchodilators

Anti-cholinergic bronchodilators are less effective than β_2-agonists in asthma because they only block cholinergic bronchoconstriction and have a slower onset of action.

Cromones

Inhaled cromones control the symptoms of asthma and effectively block bronchospasm induced by allergens, exercise, adenosine and sulphur dioxide. Cromolyn sodium and nedocromil sodium are well tolerated and have no significant side-effects (140). Due to their short-lived action, cromones must be inhaled two to four times daily and are considered inconvenient regimens for asthma (116). They appear to be most effective in patients with mild asthma, but are not effective for all patients.

Inhaled corticosteroids

The use of cortisone as an inhaled aerosol was first reported in 1951 (141) and in 1954 prednisone and hydrocortisone became standard treatments for asthma.

Beclomethasone was introduced in 1969 for topical use in skin diseases, but was later adapted for aerosol administration (1972) and assumed an important role in the treatment of asthma (2,115).

Inhaled corticosteroids reduce inflammation and improve pulmonary function, leading to reductions in symptoms and exacerbations with an acceptable side-effect profile at the doses usually administered (142).

The introduction of guidelines for asthma therapy has led to earlier use of inhaled corticosteroids by adults and children, and increasing prescription for the long-term prophylactic treatment of asthma. With this increase in usage has come a growing concern about the safety, particularly the local and systemic side-effects, of inhaled corticosteroids. Local side-effects are caused by deposition of corticosteroids in the upper airway. These effects may be reduced by the use of a large-volume spacer that removes most of the fraction of drug that would otherwise be deposited in the oropharynx (143,144). Rinsing the mouth may reduce the local deposition associated with dry powder inhalers. Dysphonia, the most common local side effect of inhaled corticosteroids, can occur in more than 50% of patients receiving high-dose therapy (145).

Systemic side-effects result from gastrointestinal absorption of the swallowed fraction of the drug as well as through absorption from the lung (146,147). The use of a corticosteroid such as budesonide or fluticasone propionate that undergoes extensive first-pass hepatic metabolism can help to reduce side-effects from gastrointestinal absorption, as less drug enters the systemic circulation (116). With the use of such drugs, the fraction absorbed from the lung becomes the major, unavoidable source of systemic availability. While it is recognized that systemic absorption occurs following inhaled administration of corticosteroids, the dose at which clinically relevant side-effects occur is controversial. The controversy stems from the fact that the degree of systemic absorption depends not only upon the prescribed dose, but also

upon the mode and technique of delivery and the severity of the underlying disease. However, some patients will still require oral corticosteroid treatment for optimal control of their disease, and these drugs have a far greater risk of adverse effects.

An additional concern is that compliance with inhaled corticosteroids is poor (148). One strategy to improve compliance and clinical control was the introduction of fixed combinations of a steroid and a long-acting β_2-agonist (salmeterol/fluticasone and formoterol/budesonide). Combinations with long-acting β_2-agonists that have a fast onset of action and therefore symptom relief feedback, may be helpful in improving compliance. However, the fixed combinations may provide less flexibility with a potential risk of over- or under-treatment resulting from the masking effect that long-acting β_2-agonists may have on inflammation during worsening of the disease (149).

Therapeutic ratio of inhaled corticosteroids

The safety/efficacy ratio, or therapeutic ratio, of an anti-asthmatic agent is determined by the relationship between its dose–response relationship for clinical efficacy and its systemic adverse events (150). Efficacy can be measured through the use of recognised clinical endpoints such as FEV_1, $FEF_{25-75\%}$ and morning PEF. However, safety must be measured through pharmacological and pharmacokinetic parameters, combined with clinically relevant endpoints such as adverse events and biochemical and laboratory markers. While an understanding of the safety/efficacy ratio is important, it is of more value to understand the therapeutic index relative to other available anti-asthmatic agents.

The use of a relatively low dose of inhaled beclomethasone dipropionate (BDP, 336 $\mu g\,day^{-1}$) for 4 weeks in 24 patients with mild and moderate asthma improved pulmonary function and decreased the frequency of salbutamol use significantly more than inhaled placebo (151). However, these improvements were short-lived when BDP treatment was stopped. Spirometric indices of airflow obstruction decreased to baseline levels 1 week after BDP treatment was discontinued, although treatment-associated improvements in morning peak flow and salbutamol use lasted longer (151). This short 'off-treatment' effect has also been reported in other studies (64,152–156).

Despite the clear improvements in pulmonary function and rescue salbutamol use seen in this study, BDP treatment caused only a modest and statistically insignificant decrease in the percentage of eosinophils in induced sputum (151). These data suggest that although asthma symptoms are controlled by relatively low-dose inhaled BDP treatment, airway inflammation is not.

Studies showing inhaled corticosteroid treatment reduces airway inflammation have used doses of 500–1000 $\mu g\,day^{-1}$ (157–160). Such studies may not take into account the dissociation between the dose needed to decrease airway inflammation and that needed to improve clinical indices of asthma control, reduce asthma symptoms and improve airway calibre (149). It is possible that the dose–response curve for the effect of a drug on symptoms may be different from that of its effects on bronchial hyper-responsiveness or on eosinophilic inflammation of the airways.

Reduction in airway calibre affects the bioavailability of inhaled drugs and reduces peripheral drug delivery (68,161,162). Either increasing the dose or improving drug delivery could theoretically overcome the reduced bioavailability of inhaled medication.

The impact of air-trapping on the use of inhaled corticosteroids

The presence of air-trapping in asthma limits the potential for inhaled therapies to reach the site of inflammation, and in particular, the small airways.

Radiographic techniques have been used in patients with mild to moderate asthma to compare the efficacy of an extra-fine hydrofluoroalkane (HFA)-propelled corticosteroid aerosol (HFA-BDP) that is well deposited in the lung periphery, with a conventional chlorofluorocarbon (CFC)-propelled aerosol that does not penetrate the smaller airways (CFC-BDP) (84). After 4 weeks of treatment the HFA-BDP aerosol resulted in significantly more improvement in air-trapping overall compared with CFC-BDP. No significant difference was observed between the groups with respect to symptoms or spirometric measurements. These findings suggest that newer agents targeting the small airways may improve airway function. These changes may be clinically relevant in terms of associated improvement in subjective measurements that are not paralleled by detectable improvement in conventional physiological measures such as FEV_1. Consequently, the deeper penetration of the newer inhaled therapies into the lung necessitates the development of techniques that enable the effect in the smaller airways to be monitored.

The effect of inhaled corticosteroids on the small airways

The presence of inflammation in the small airways in asthma has therapeutic implications, as it is not clear whether inhaled corticosteroids effectively treat this compartment of the lung. Inhaled corticosteroid therapy has been shown to decrease inflammation in the proximal airways (163,164) but may not be as efficient in the smaller airways (18,160,165). Despite the use of inhaled corticosteroids, patients with chronic asthma may exhibit significant small airway inflammation (165) and persistence of their asthmatic symptoms (166); of those patients complying with regular prophylactic therapy, 56% still reported asthma symptoms (167). The persis-

tence of inflammation in the peripheral airways of patients with asthma treated with inhaled corticosteroids could result in fibrotic changes and fixed airway obstruction in the peripheral lung in the later stages of this disease (97,99,168).

From the evidence that inflammatory and structural changes occur throughout the airways, it is clear that anti-inflammatory treatment should be directed at both the large and small airways to achieve suppression of inflammation throughout the entire bronchial tree. However, not all metered-dose inhalers and dry powder inhalers are efficient at specifically depositing medication in the peripheral airways of the lung (99,169,170). Ventilation scans indicate that in asthma, much greater aerosol deposition occurs in central airways relative to peripheral airways (10). Even with optimal inhalation techniques only 10% of the corticosteroid dose generated by CFC-based inhalers reaches the lower respiratory tract with most medication deposited in the oropharynx (52,171,172).

One method that has been employed to overcome the problem of drug delivery to the airways is to alter the propellant used and hence particle size. Analysis of the site of deposition of particles within the airway in asthma suggests that particles of the 3–5 μm range target the large, central airways and that particles in the range of 1·5–3 μm are needed to reach the peripheral airways (170). However, 70% of the particles emitted from a standard CFC-metered dose inhaler are larger than 5 μm (52). The use of a HFA formulation of corticosteroids results in a propellant that in some cases delivers an aerosol with a smaller mean particle size than that generated by conventional CFC-based metered dose inhalers (80). The particle size of HFA-BDP is 1·1 μm, three times smaller than that with the conventional CFC-BDP propellant. This formulation has been shown to result in better lung deposition than the CFC formulation; approximately 60% of the BDP dose is deposited in the lung using a HFA propellant (173). The use of HFA-propelled BDP has also been reported to result in a reduction in the number of asthma exacerbations, even at a lower dose of inhaled corticosteroid, than CFC-propelled BDP (16·9% *vs*. 22·7% respectively) (174), and 40% fewer discontinuations from exacerbations than CFC-propelled BDP (175). These findings are consistent with the hypothesis that treatment of the small airways may decrease asthma exacerbation rates. HRCT scanning has shown that HFA-corticosteroid aerosols have greater efficacy than the same dose of the larger particle size CFC-corticosteroid aerosol on small airways function, most likely due to the more effective delivery to the lung periphery (80). The downside to enhanced delivery to the small airways may be an increased incidence of side-effects due to the increased concentration of the drug being absorbed from the lung and increased systemic bioavailability of drug. While dose-related effects of corticosteroids on the surrogate markers of inflammation have been demonstrated in patients with mild to moderate asthma, higher doses (800–1600 μg day^{-1}) are associated with adrenal suppression and a decrease in the therapeutic index (176). It has been recommended that with doses in excess of 800 μg day^{-1}, a large-volume spacer device is used to lessen local adverse effects and reduce systemic absorption (177).

While HFA-propelled BDP may provide greater deposition, the involvement of the small airways means that small luminal calibres or closed airways may be present. This will have the effect of decreasing peripheral deposition even when modern devices and improved inhalation techniques are used.

THE RENAISSANCE OF ORAL/ SYSTEMIC THERAPY?

Traditional systemic drugs, such as the oral corticosteroids, are potent but non-specific anti-inflammatory drugs, as indicated by their action at a number of physiological sites. Thus, to avoid unacceptable systemic side-effects, corticosteroids should be given locally via inhalation. The drawback of inhaled therapy is that it does not reach all the anatomical regions of the lung. Since metered-dose inhalers deliver most of the dose to the central airways (178), it is likely the peripheral airways will not be affected. Delivery of an anti-inflammatory drug to the small airways via the pulmonary blood supply may be a better approach in the treatment of asthma since this will target not only the epithelial cells of the airway, but also the smooth muscle and other adventitial cells. This is especially important in the peripheral airways where the focus of inflammation appears to be localized deeper in the tissue compared with the larger airways (93). In addition, the use of inhaled therapies means that the systemic aspect of asthma, which affects areas other than the lung, are not treated.

Compliance with long-term regimens is a known problem, particularly when the symptoms are controlled. With asthma therapy, non-compliance is generally estimated to be around 10–46% (179). However, studies have shown that better compliance is achieved with oral than with inhaled therapy (180), as many patients prefer tablets to inhalers (179) and a simplified treatment regimen. Oral medication may also control concomitant allergic conditions such as rhinitis and atopic dermatitis.

Leukotriene receptor antagonists represent a new class of systemically or orally administered drugs that have a more disease-specific mode of action. The cysteinyl leukotrienes (Cys-LTs) are lipid mediators generated from the metabolism of arachidonic acid and play an important role in the pathogenesis of asthma (181,182). This role lies in the process of asthmatic inflammation that results in bronchoconstriction, bronchial hyper-respon-

siveness, hypersecretion of mucus and mucosal oedema (181). They may also induce aspects of the chronic remodelling response seen in asthma. They are only produced during the disease process and so blockade of the Cys-LT receptor is not associated with disturbance of normal physiological function. Only the effects of leukotrienes are blocked and thus disease-specific mediators are being targeted. Therefore, the leukotriene receptor antagonists may be given systemically without interfering with normal physiological function.

Given systemically the leukotriene receptor antagonists reach the large and small airways, as well as having an effect on the other systemic disease-specific involved in asthma, including the nose and bone marrow (183). Expression of leukotriene receptors has been shown on a number of different cells, not only in lung tissue, but also in progenitor stem cells in bone marrow (184). They have also been shown to have beneficial effects on the established clinical correlates of small airway function in both adults and children (185–187).

Other examples of new therapeutic principles for asthma are the use of anti-IgE antibodies. There is a clear association between elevated levels of IgE and clinical disease. It has been demonstrated that systemically administered anti-IgE reduces levels of IgE and results in clinical improvements of asthma. A recombinant humanised monoclonal antibody that forms complexes with free IgE has been shown to block the interaction of IgE with mast cells and basophils (188). In early clinical investigations, this antibody attenuated the early-phase and late-phase airway-obstructive response to challenge by allergen and suppressed the accumulation of eosinophils in the airway (189,190). Subsequent evaluation showed that regular intravenous administration of this preparation to patients with moderate or severe allergic asthma controlled symptoms better than placebo and allowed a clinically significant reduction in the dose of oral and inhaled corticosteroids (188). Also, therapy was well tolerated with few side-effects despite the drug being given systemically (188).

Specific cytokine antagonists, inhibitors of T cell function, selective inducible nitric oxide synthase inhibitors, and even gene-directed strategies such as DNA vaccines are other examples of an evolving area of novel therapeutic approaches to treat the inflammation in asthma (191,192).

The future direction in treating asthma is likely to be a systemically administered medication that has few side-effects and is targeted specifically to the pathogenesis of asthma (117). In addition to reaching the small airways of the lung an ideal drug therapy for asthma should target disease-specific mediators. The leukotriene receptor antagonists are representatives of this new class of drugs and we look forward to an exciting future for the treatment of asthma as other drugs emerge.

CONCLUSIONS

Although it has been known for many years that asthma is an inflammatory disorder, there is now accumulating evidence that inflammation and other pathophysiological changes in the small airways are important in all stages of asthma (18,52,87,88,93). Therefore, to achieve suppression of inflammation throughout the lung, treatment should be directed at both the large and small airways. Control of inflammation in the small airways is particularly critical in early stages of asthma (110).

The difficulty in measuring changes in the small airways due to the lack of specificity, sensitivity and consistency of pulmonary function tests has resulted in the considerable under-estimation of the role of these airways in asthma. Newer HRCT techniques have led to advances in our ability to assess abnormalities in the small airways, but despite this there is still no single method that sufficiently measures small airways function. Clinicians therefore need to consider a combination of objective measures and clinical correlates when evaluating their patients' condition.

Current understanding defines asthma as an inflammatory disease. However, recent evidence suggests that the inflammatory process extends to the most distal parts of the lung and even beyond, involving the systemic components such as the nose and bone marrow (24,25,29,30,33). The view that asthma is a systemic disorder supports the use of systemic therapies for asthma (46).

While the initial approach to treating asthma was systemic, the early oral therapies were associated with serious side-effect profiles. Consequently, inhaled therapies were developed in an attempt to decrease the systemic side-effects. However, inhaled therapies, such as the corticosteroids, have a non-specific anti-inflammatory effect and may affect a number of organs apart from the lung. Such effects result from the gastrointestinal and pulmonary absorption of the inhaled drug (140,147).

Although inhaled therapies decrease inflammation in the large airways they may not be as efficient in treating small airways inflammation (18,160,165). The majority of the inhaled dose is deposited in the central airways and only a small proportion reaches the peripheral airways (52,87,172). In addition, inhaled therapies do not treat the systemic aspect of asthma.

Since asthma is now understood to be both a systemic and small airways disease, a treatment is needed which is systemically or orally administered, is able to reach the small airways and targets disease-specific mediators, both in the lung and systemically, without affecting normal physiological functions.

The leukotriene receptor antagonists are representatives of a new class of drugs for treatment of asthma that offer this new approach. Anti-IgE and cytokine antagonists are further examples, and the arrival of other new

therapeutic strategies is awaited. The future for asthma therapy is likely to focus on targeting a combination of disease-specific mediators to achieve optimal disease outcomes in asthma.

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